Agenzia Italiana del Farmaco
AIFA

Workshop on
HEART FAILURE
Rome, November 24-25, 2013

Reimbursement policies in Europe:

Values and Limits

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25 November 2013

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Public Declaration of transparency/interests*

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Interests in pharmaceutical industry	NO	Currently	Last 2 years	More than 2 years but less than 5 years ago	More than 5 years ago (optional)
Direct interests:					
Employment with a company	X				
Consultancy for a company	X				
Strategic advisory role for a company	X				
Financial interests	X				
Ownership of a patent	X				
Indirect interests:					
Principal investigator	X				
Investigator	X				
Individual's Institution/Organisation receives a grant or other funding	X				

***Paolo Daniele Siviero** in accordance with the Conflict of Interest Regulations approved by AIFA Board of Directors (26.01.2012) and published on the Official Journal of 20.03.2012 according to 0044 EMA/513078/2010 on the handling of the conflicts of interest for scientific committee members and experts

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Heart failure: an increasing problem for global healthcare systems

Figure 1.1a **Deaths by cause, men, latest available year, Europe**

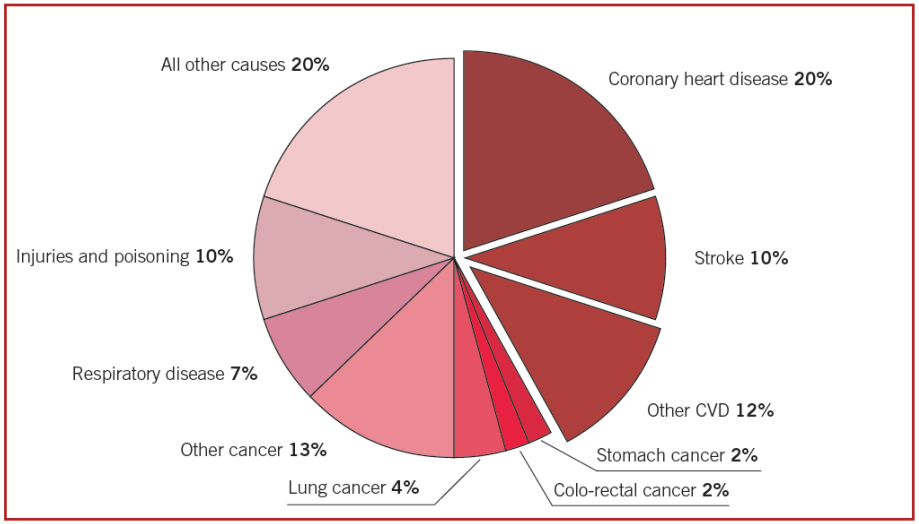
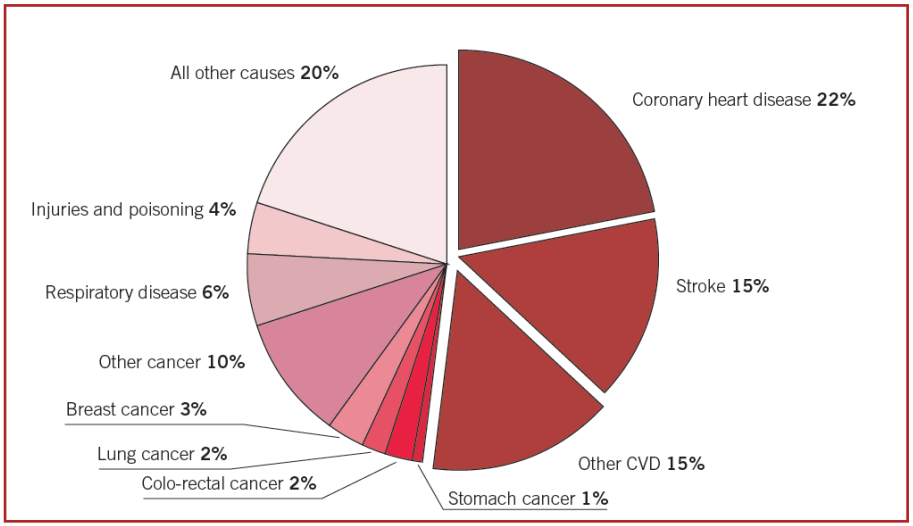


Figure 1.1b **Deaths by cause, women, latest available year, Europe**



EuroHeart II
BUILDING ACTION on HEART DISEASE and STROKE

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European Cardiovascular Disease Statistics. 2012 Edition

Heart failure: an increasing problem for global healthcare systems

Figure 1.1a Deaths by cause, men, latest available year, Europe

Figure 1.1b Deaths by cause, women, latest available year, Europe

- Each year cardiovascular disease (CVD) causes over 4 million deaths in Europe and over 1.9 million deaths in the European Union (EU).
- CVD causes 47% of all deaths in Europe and 40% in the EU.
- CVD is the main cause of death in women in all countries of Europe and is the main cause of death in men in all but 6 countries.

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Heart failure: an increasing problem for global healthcare systems

Table 12.1 Total cost of CVD, CHD and cerebrovascular diseases, 2009, EU

	CVD		CHD		Cerebrovascular disease	
	€ thousands	% of total	€ thousands	% of total	€ thousands	% of total
Direct health care costs	106,156,940	54%	19,867,875	33%	19,102,868	50%
Productivity loss due to mortality	26,963,326	14%	12,014,249	20%	4,812,409	13%
Productivity loss due to morbidity	18,873,665	10%	5,530,552	9%	3,329,282	9%
Informal care costs	43,560,202	22%	22,812,144	38%	11,115,782	29%
Total	**195,554,133**		**60,224,820**		**38,360,340**	

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Heart failure: an increasing problem for global healthcare systems

Table 12.1 **Total cost of CVD, CHD and cerebrovascular diseases, 2009, EU**

- Overall CVD is estimated to cost the EU economy almost €196 billion a year.
- Of the total cost of CVD in the EU, around 54% is due to health care costs, 24% due to productivity losses and 22% due to the informal care of people with CVD.

Direc costs				60%
Produ to mo				13%
Produ to mo				9%
Infor				29%
Total	195,554,133	60,224,820	38,360,340	

EuroHeart II BUILDING ACTION on HEART DISEASE and STROKE

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Expenditure for cardiovascular drugs in Italy

Categoria terapeutica	Classe A-SSN^		Acquisto private di classe A		Classe C con ricetta		Automedicazione SOP e OTC		Strutture Sanitarie Pubbliche		Totale
	euro°	%*	euro°	%*	euro°	%*	euro°	%*	euro°	%*	euro°
C- Cardiovascolare	3.813	87,7	157	3,6	89	2,0	125	2,9	167	3,8	4.350
A- Gastrointestinale e metabolismo	1.907	55,5	174	5,1	237	6,9	651	19,0	465	13,5	3.434
L- Antineoplastici e immunomodulatori	260	7,8	20	0,6	9	0,3	-	-	3.034	91,3	3.323
N-SNC	1.426	43,1	131	4,0	946	28,6	253	7,6	553	16,7	3.310
J- Antimicrobici	884	33,4	131	4,9	87	3,3	<1	<0,1	1.543	58,3	2.645
B- Sangue e organi emopoietici	593	30,4	77	4,0	93	4,8	13	0,7	1.174	60,2	1.950
R- Respiratorio	1.059	61,0	111	6,4	159	9,2	354	20,4	52	3,0	1.734
M- Muscolo-scheletrico	506	38,5	176	13,4	213	16,2	333	25,3	86	6,6	1.315
G- Genito-urinario e ormoni sessuali	400	32,4	33	2,7	652	52,8	48	3,9	102	8,3	1.235
D- Dermatologici	57	8,8	37	5,8	271	42,0	258	39,9	23	3,5	646
H- Ormoni sistemici	230	41,2	47	8,4	26	4,6	-	-	256	45,7	559
S- Organi di senso	212	38,0	17	3,0	172	30,8	91	16,3	67	11,9	558
V- Vari	104	23,9	<1	<0,1	44	10,0	<1	<0,1	370	84,4	438
P- Antiparassitari	12	56,5	3	13,6	4	19,6	1	4,7	1	5,5	21
Totale	**11.463**	**44,9**	**1.032**	**4,0**	**3.000**	**11,8**	**2.128**	**8,3**	**7.892**	**30,9**	**25.515**

^Spesa di fascia A al netto della fascia C rimborsata per i titolari di pensione di guerra diretta vitalizia ai sensi della Legge n. 203 del 19 luglio 2000 (25 milioni di euro)
° Lorda in milioni di euro
*Calcolata sulla categoria
Fonte: OsMed, Tracciabilità del farmaco ed elaborazione OsMed su dati IMS Health

Expenditure for cardiovascular drugs in EU

ATC	Italia	Austria	Belgio	Finlandia	Francia	Germania	Greecia	Irlanda	Portogallo	Spagna	Uk
C - Cardiovascolare	24,7	18,3	18,4	11,1	17,0	11,6	31,5	15,3	27,9	18,2	12,4
A - Gastrointestinale	17,8	14,1	12,7	18,4	13,1	13,6	15,5	20,7	17,4	15,9	16,5
N - SNC	14,2	16,5	17,3	17,6	14,9	14,6	14,8	19,6	17,3	19,7	25,6
R - Respiratorio	11,3	10,4	13,4	13,3	10,7	9,9	9,2	11,7	9,4	14,5	18,6
G - Genito-urinario e ormoni sessuali	6,7	4,4	5,4	6,9	4,2	4,8	2,7	4,6	6,4	7,9	6,0
J - Antimicrobici	6,5	9,8	10,0	3,7	10,7	9,0	6,5	3,3	5,6	3,2	2,6
M - Muscolo-scheletrico	5,3	4,7	3,5	3,6	3,8	3,7	4,3	3,3	6,7	5,1	2,5
D - Dermatologici	3,9	3,0	2,6	2,6	2,8	3,1	2,3	3,0	2,9	3,4	5,6
B - Ematologici	3,3	4,7	3,9	6,7	7,5	8,0	5,6	3,0	2,7	3,5	2,0
S - Organi di senso	3,2	1,2	1,4	2,2	3,6	2,6	2,0	1,8	2,3	3,0	2,8
H - Ormoni sistemici	1,3	1,4	1,8	1,8	1,9	1,9	1,5	1,6	0,6	1,8	2,3
L - Antineoplastici	1,2	10,3	8,7	11,8	9,1	14,4	3,6	11,6	0,4	3,1	2,4
V - Vari	0,4	1,0	0,4	0,2	0,5	2,6	0,4	0,3	0,2	0,5	0,2
P - Antiparassitari	0,1	0,1	0,2	0,2	0,3	0,2	0,1	0,3	0,2	0,1	0,4

* Il valore di spesa comprende i farmaci di classe A-SSN (pubblico + privato), di classe C con ricetta e i farmaci di automedicazione (SOP e OTC)

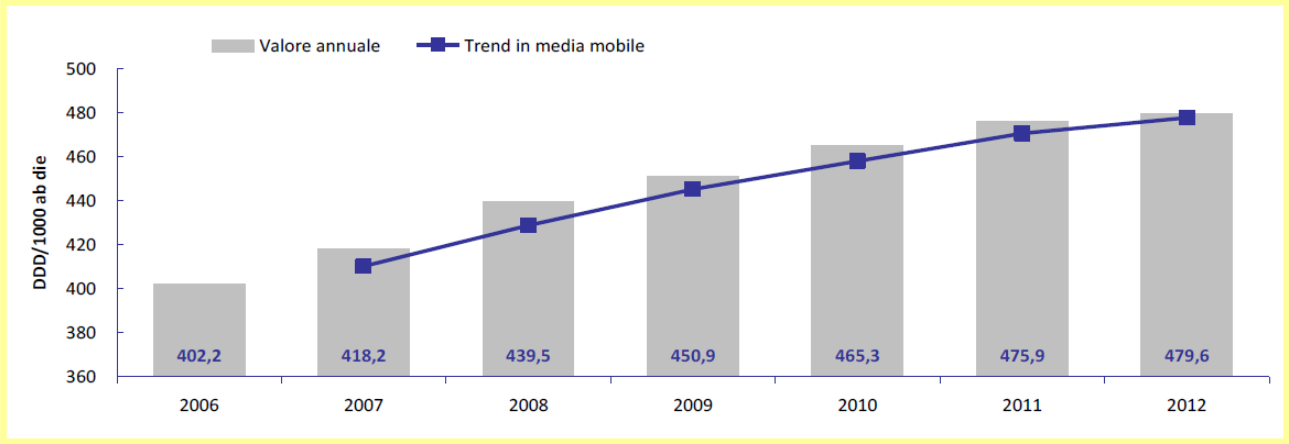
Fonte: elaborazioni AIFA su dati IMS/MIDAS

Temporal trend in expenditure for cardiovascular drugs in Italy

PRINCIPALI INDICI DI SPESA, DI CONSUMO E DI ESPOSIZIONE
APPARATO CARDIOVASCOLARE

Spesa pubblica* in milioni di € (% sul totale)	**3.980,0**	**(20,6)**
Δ % 2012/2011		-12,4
Range regionale spesa lorda pro capite (€):	49,5	77,2
DDD/1000 ab die (% sul totale)	**479,6**	**(41,5)**
Δ % 2012/2011		0,7
Range regionale DDD/1000 ab die:	372,4	559,8

* spesa convenzionata e spesa per farmaci acquistati dalle strutture sanitarie pubbliche



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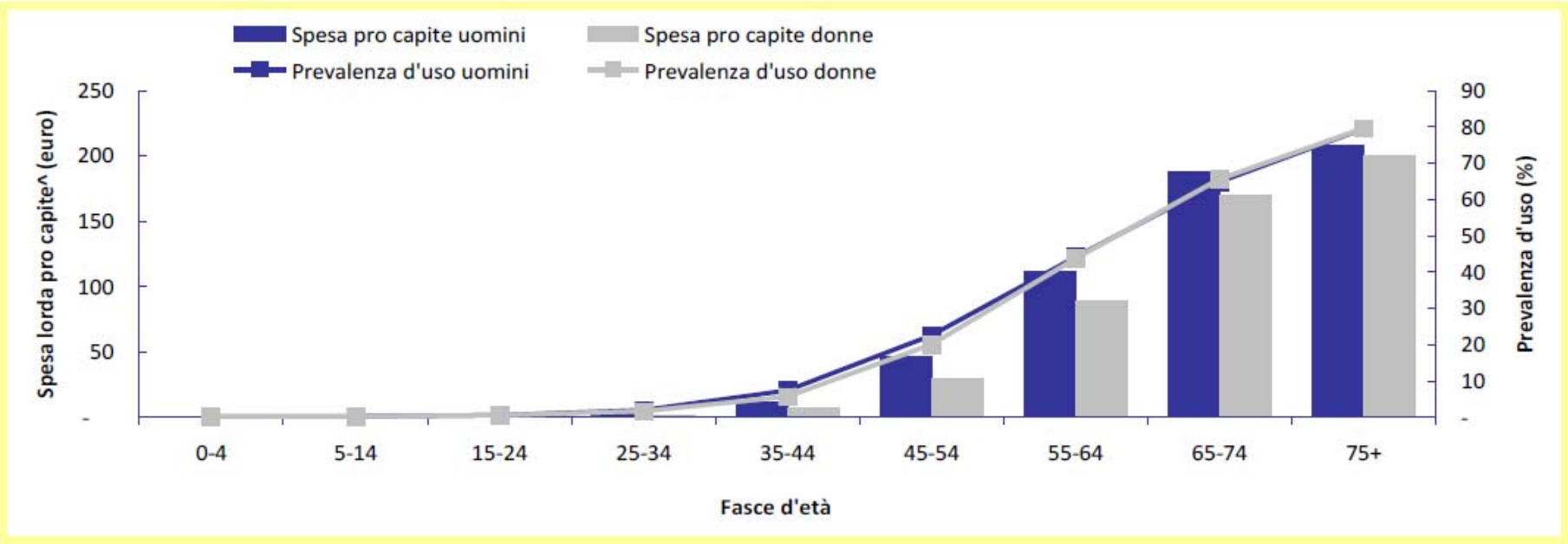
Expenditure for cardiovascular drugs in Italy by gender



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Ranking of SSN expenditure by cardiovascular drugs (Atc1=C)

Rank	Atc2	SSN Expenditure 2013 (extimation)	%
1	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM (C09)	1.262.766.836	43,9%
2	LIPID MODIFYING AGENTS (C10)	871.260.072	30,3%
3	CALCIUM CHANNEL BLOCKERS (C08)	244.481.477	8,5%
4	BETA BLOCKING AGENTS (C07)	194.068.947	6,7%
5	CARDIAC THERAPY (C01)	148.415.462	5,2%
6	DIURETICS (C03)	82.000.645	2,8%
7	ANTIHYPERTENSIVES (C02)	75.544.999	2,6%
8	VASOPROTECTIVES (C05)	298.702	0,0%
9	PERIPHERAL VASODILATORS (C04)	110.315	0,0%
10	TOTAL	2.878.947.455	100%

Source: Centro Studi AIFA on Sfera data

Economic sustainability and affordability

https://www.asdreports.com/news.asp?pr_id=1325

New oral anticoagulants: a paradigm for a balance between values and limits

Values

- Fixed oral dosing
- No need to monitor prothrombin time or INR
- Fewer drug interactions
- No dietary restrictions

Limits

- Lack of validated tests to assay their anticoagulant effect
- No antidote readily available to halt bleeding
- Lack of data on long-term adverse effects beyond bleeding
- Absence of head-to-head comparisons between novel oral anticoagulants
- Costs

New oral anticoagulants

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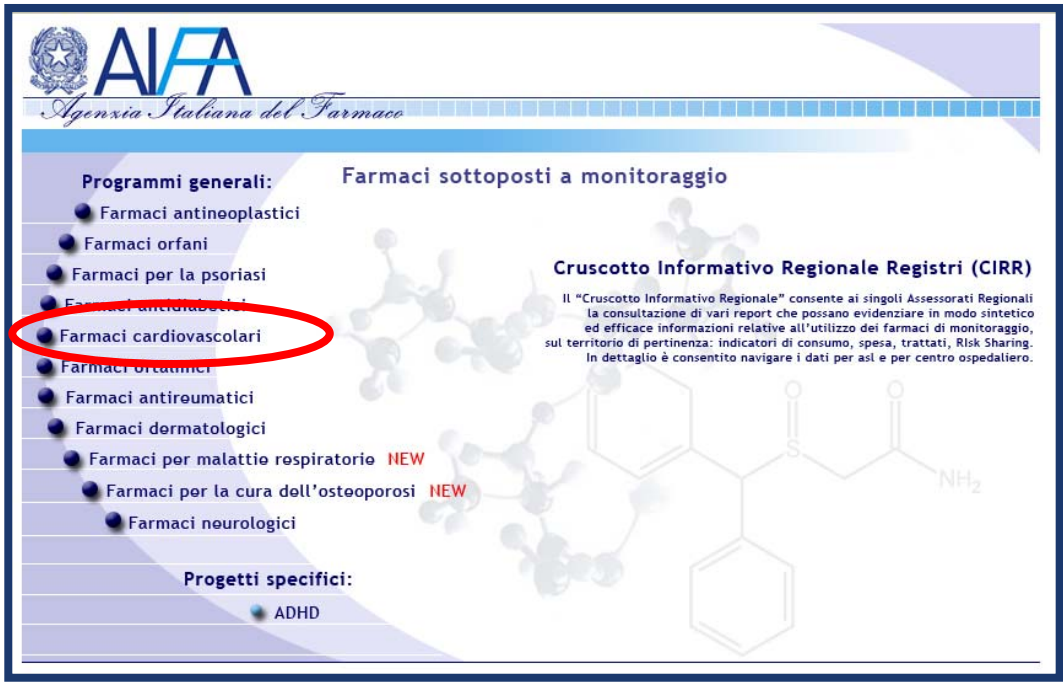
26/09/2012

AIFA CONCEPT PAPER

I nuovi anticoagulanti orali nella prevenzione di ictus e tromboembolismo sistemico in pazienti con fibrillazione atriale non valvolare.

Preparazione del Draft	10.08.2012
Approvazione del Draft e rilascio per la consultazione	26.09.2012
Inizio della consultazione	01.10.2012
Fine della consultazione	01.12.2012



AIFA Registries on cardiovascular diseases

Drug	Starting data	Setting	Inclusion	N° of treatments*
Pradaxa®	16/06/2013	FANV	[CHA2 DS2-VASc≥1 AND HAS-BLED>3] OR [TTR<70% in the last 6 months] OR [Unable to perform INR monitoring]	32056
Rivaroxaban ®	13/09/2013	Persistent FANV	[CHA2 DS2-VASc≥3 AND HAS-BLED>3] OR [TTR<60% in the last 6 months] OR [Unable to perform INR monitoring]	4229
Apixaban ®	Upcoming	Chronic or parossistic FANV	[CHA2 DS2-VASc≥3 AND HAS-BLED>3] OR [TTR<70% in the last 6 months] OR [Unable to perform INR monitoring]	n.a.

* Updated at 15/11/2013

Expenditure for antithrombotic drugs in italy compared with other EU nations

Jan-Sep 2013. Incidence of antithrombotic agents (B01A)

Country	ITALY RETAIL		FRANCE RETAIL		GERMANY RETAIL		SPAIN RETAIL		UK RETAIL	
Atc4	Standard Units (%)	Outpatient Expenditure (%)	Standard Units (%)	Outpatient Expenditure (%)	Standard Units (%)	Outpatient Expenditure (%)	Standard Units (%)	Outpatient Expenditure (%)	Standard Units (%)	Outpatient Expenditure (%)
B01AC Platelet aggregation inhibitors excl. heparin	71,7%	36,6%	55,8%	26,8%	71,7%	23,1%	51,6%	24,2%	48,6%	28,6%
B01AA Vitamin K antagonists	9,3%	2,6%	13,5%	2,2%	9,4%	2,0%	10,7%	2,8%	23,2%	9,9%
B01AB Heparin group	2,0%	36,5%	1,7%	21,1%	1,8%	25,2%	2,1%	39,4%	0,3%	25,8%
B01AX Other antithrombotic agents	0,1%	1,5%	0,2%	3,9%	0,1%	1,8%	0,0%	0,2%	0,0%	0,2%
B01AE Direct thrombin inhibitors	0,1%	0,5%	2,7%	5,9%	1,5%	6,1%	1,3%	6,0%	0,3%	4,8%
B01AF Direct factor Xa inhibitors	0,0%	0,1%	1,5%	6,6%	2,6%	19,1%	0,5%	4,1%	0,2%	4,6%
B01AD Enzymes	0,0%	0,0%	0,0%	0,0%	0,002%	0,3%	0,0%	0,0%	0,0%	0,0%
Others	16,9%	22,2%	24,6%	33,4%	13,0%	22,4%	33,8%	23,3%	27,4%	26,1%
Total Blood and blood forming organs (B)	**100,0%**	**100,0%**	**100,0%**	**100,0%**	**100,0%**	**100,0%**	**100,0%**	**100,0%**	**100,0%**	**100,0%**

Source: *Aifa on Midas International database*

When does HTA matter?

HTA analysis for supporting pricing & reimbursement decisions

HTA analysis for evaluating risk-benefit profile

HTA in the appropriateness of utilization

HTA analysis for supporting pricing & reimbursement re-negotiation

HTA analysis for supporting decision of new therapeutic indications

HTA analysis for assessing risk-benefit profile following adverse events signals

Major challenges in evaluating heart failure RCT according to an HTA perspective

1) Complexity of disease:

- Heart failure is a complex syndrome that can result from any structural or functional cardiac disorder which impairs the ability of the heart to function as a pump to support a physiological circulation.
- The evaluation of a patient with suspected heart failure therefore entails more than determining whether or not the syndrome is present – it also requires an identification of the underlying abnormality of the heart.
- Higher prevalence in elderly (potential impact of co-morbidity and co-medication).
- Great heterogeneity in different countries/structures in diagnostic and therapeutic approach to HF.

Major challenges in evaluating heart failure RCT according to an HTA perspective

2) Diagnosis: to determine the most clinically effective and cost-effective diagnostic algorithms considering

- Symptom or sign
- Clinical features
- Electrocardiography (ECG)
- B-type natriuretic peptides (BNP)
- N-terminal pro-B-type natriuretic peptides (NT-proBNP)
- Echocardiography
- Other cardiac imaging (TOE, CRM, SPECT, PET)
- Other investigations (cardiac catherization, genetic testing)

ESC Guidelines for the Diagnosis and Treatemtn of acute and chronic heart failure 2012 Eu Heart J 2012

Major challenges in evaluating heart failure RCT according to an HTA perspective

3) Population:

- Representativeness (*e.g.* gender, elderly, race)
- Comorbidities
- Stratification

4) Intervention and comparator:

- Placebo in add-on design (*caveat*: local SOC may differ substantially)
- Active-control studies
- Combination therapy

Major challenges in evaluating heart failure RCT according to an HTA perspective

5) End point	Notes
Mortality	All-cause vs cause specific death
Heart failure hospitalization	Need for a consistent definition and accurate adjudication of cause-specific hospitalization
Duration of hospitalization	Include both number of days in intensive/coronary units and in total in-patient stay
Repeated hospitalization	Need to standardize critaria for hospitalization
Days alive and out of hospital	– Limitation in its ability to weight the relative importace of deaths vs repeat hospitalization – The “win ratio” as a approach to the analysis of composite end-point based on clinical priorities

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Zannad F et al. Eur J Heart Fail 2013
EMA Guidance CHMP/EWP/2986/03 Rev.1
Pocock SJ et al Eur Heart J 2012

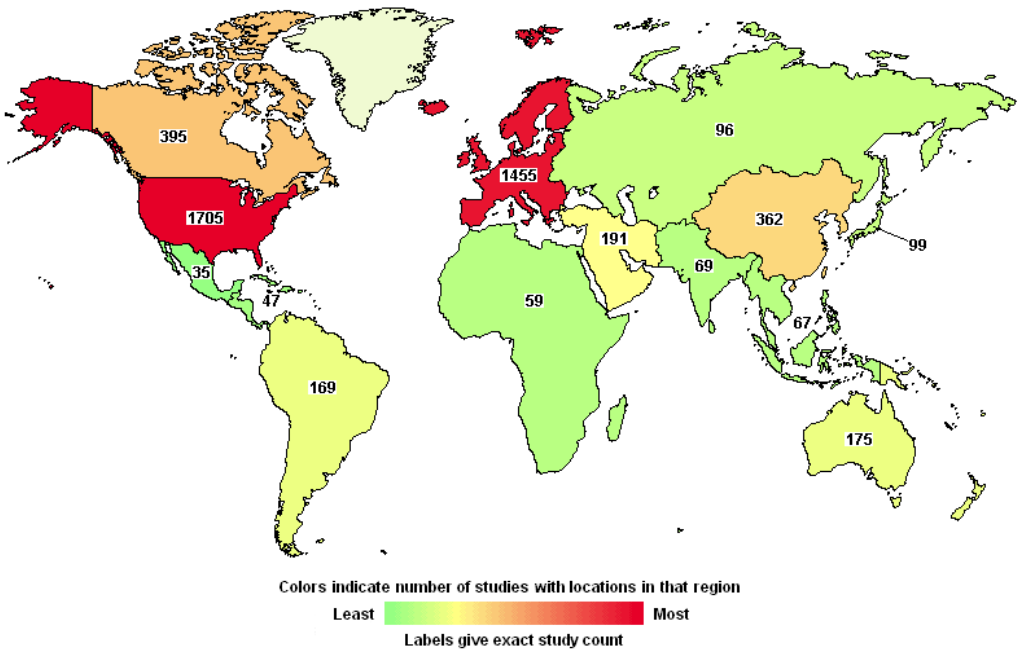
Major challenges in evaluating heart failure RCT according to an HTA perspective

5) End point (CONT'D)	Notes
Symptoms (e.g. dyspnoea)	Need for consistent measures and standardized methods
Patient Reported Outcomes	Need for consistent and validated measures given its relevance for pharmacoeconomic evaluation
Changes in resources utilization	Concomitatn medication, oxygen therapy and intubation/assistend ventilation
Other terminal events	Consider potential for LVAD implantation, heart transplant

Zannad F et al. Eur J Heart Fail 2013
EMA Guidance CHMP/EWP/2986/03 Rev.1
Pocock SJ et al Eur Heart J 2012

Clinical trial on heart failure

ClinicalTrials.gov 4059 RCT registered



Available at: www.clinicaltrials.gov (accessed on 20/11/2013)

Looking to the future: “rising from the doldrumd in acute heart failure”?

- Recombinant human relaxin-2 (Sarelaxin®): under evaluation at the EMA[1]
- Genetically targeted enzyme replacement therapy (Mydicar®) [2]
- New types of assistance: telemonitoring support[3]

[1]Konstam MA. Lancet 2013; Teerlink JR et al. Lancet 2013; Metra M et al. J Am Coll Cardiol 2013

[2]Papolos A, Frishman WH. Cardiol Rev 2013

[3]Pandor A et a. HTA 2013

Is it an unbridgeable gap?

How to bridge the gap

- Collaboration and communication between stakeholders (research centers, patients and physicians associations, regulators, payers and pharmaceutical industry);
- Design together (Regulators, Payers, Manufacturers, University, Patients) clinical trials to obtain homogenous and forecasting decisions;
- Stimulating high quality research (defining consistent and transparent quality standards; harmonizing clinical trial procedures, defining endpoints for added clinical benefit in view of HTA);
- Promoting “scientific advice” model in the process of R&D shared by the Regulator and the Payer.

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